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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/845,160	05/01/2001	Hiroyuki Mizuguchi	081356-0163	2644

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EXAMINER
WINKLER, ULRIKE

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 08/26/2003

16

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/845,160	Applicant(s) MIZUGUCHI ET AL.	
	Examiner Ulrike Winkler	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *June 16, 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Amendment filed June 16, 2003 (Paper No. 15) in response to the Office Action of October 2, 2002 and the subsequence Non-Responsive letter sent May 20, 2003 is acknowledged and has been entered. Claims 1-20 are pending and are currently being examined.

Note: claims 19 and 20 were previously entered with the response filed February 3, 2003 (Paper No.13).

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 102

The rejection of claims 1, 3-6, 9, 11-14 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Dmitriev et al. (Journal of Virology, 1998) **is maintained** for reason of record.

Applicant's arguments filed June 16, 2003 (Paper No. 15) have been fully considered but they are not persuasive. The arguments are that the method of preparing the mutant adenovirus disclosed by Dmitriev et al. differs from the method disclosed in the instant invention. However, the claims are broadly drawn to a method of constructing a fiber mutant adenovirus vector comprising the step of inserting a restriction enzyme site. Applicant argues that the prior at utilizes extra steps not contemplated by the instant invention, specifically applicant argues that the prior art utilizes a shuttle vector and homologous recombination in a special strain of *E. coli* to achieve the insertion of the oligonucleotide sequence into the fiber HI loop.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., that the oligo DNA encoding the polypeptide of interest is introduced directly into the fiber HI loop or the specific method steps) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

To reiterate, the instant invention is drawn to a product and a method of making the product. The product is an adenovirus fiber mutant whereby a unique restriction site is inserted into the gene sequence coding for the fiber HI loop allowing for the insertion of foreign peptides into the loop region.

Dmitriev et al. disclose a method of producing a recombinant adenovirus that will have altered tropism by inserting a unique restriction site (EcoRV) into the fiber HI knob of the adenovirus. The EcoRV site was previously designed into the shuttle vector and the restriction site is not normally present in the fiber H1 loop (see construction of plasmid in material and methods). The reference discloses incorporating the tripeptide RGD into the peptide of the HI loop of the recombinant adenovirus (see material and methods). The sequence encoding the tripeptide is inserted into the fiber sequence using the unique restriction site that was engineered into the virus. The ability of the virus to infect cells that do not posses the coxsackievirus and adenovirus receptor (CAR) was tested. Experiments showed that in this model Ad-RGD fiber was able to direct levels of transgene expression 2-3 orders of magnitude higher than those mediated by control virion containing unmodified fibers. Therefore, the instant invention is anticipated by Dmitriev et al.

Claim Rejections - 35 USC § 103

The rejection of claims 1-18 and newly added claims 19-20 under 35 U.S.C. 103(a) as being unpatentable over Dmitriev et al. (Journal of Virology, 1998) in view of Arap et al. (Science, 1998) **is maintained** for reason of record.

Applicant's arguments filed June 16, 2003 (Paper No. 15) have been fully considered but they are not persuasive. The arguments are that the method of preparing the mutant adenovirus disclosed by Dmitriev et al. differs from the method disclosed in the instant invention. However, the claims are broadly drawn to a method of constructing a fiber mutant adenovirus vector comprising the step of inserting a restriction enzyme site. Applicant argues that the prior at utilizes extra steps not contemplated by the instant invention, specifically applicant argues that the prior art utilizes a shuttle vector and homologous recombination in a special strain of *E. coli* to achieve the insertion of the oligonucleotide sequence into the fiber HI loop.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., that the oligo DNA encoding the polypeptide is introduced directly into the fiber HI loop or the specific methods steps) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

To reiterate, the instant invention is drawn to a product and a method of making the product. The product is an adenovirus fiber mutant whereby a unique restriction site is inserted into the gene sequence coding for the fiber HI loop allowing for the insertion of foreign peptides into the loop region. The unique restriction sites are Csp45I and/or ClaI (claims 2, 10, 18).

Dmitriev et al. teach a method of producing a recombinant adenovirus that will have altered tropism by inserting a unique restriction site (EcoRV) into the fiber HI knob of the adenovirus. The EcoRV site was previously designed into the shuttle vector and the restriction site is not normally present in the fiber H1 loop (see construction of plasmid in material and methods). The reference discloses incorporating the tripeptide RGD into the peptide of the HI loop of the recombinant adenovirus (see material and methods). The sequence encoding the tripeptide is inserted into the fiber sequence using the unique restriction site that was engineered into the virus. The reference does not teach utilizing the Csp45I and/or ClaI restriction sites of the tripeptide NGR.

Arap et al. teach a phage a display library to screen peptides that home to tumors. Endothelial cells in the angiogenic vessels within solid tumors express several proteins that are absent or barely detectable in established blood vessels, including alpha integrins and receptors for certain angiogenic growth factors (see intro). To determine whether *in vivo* selection could be used to target tumor blood vessels, we injected phage peptide libraries into the circulation of nude mice bearing human carcinoma xenografts. Recovery of phage from the tumors led the identification of peptide motifs that targeted the phage into the tumors. One motif contained the sequence RGD sequence and another motif contained NGR. Two other sequences containing the NGR were also tested. Tumor homing for all three peptides was independent of the tumor type and species (page 377, 3rd column, 1st paragraph). The homing ratio of the phage displaying the NGR motif was three times that of the RGD-4C phage (page 378, 1st column, 1st paragraph). It is expected that the NGR and RGD-4C motif target human vasculature as well, because the NGR phage binds to blood vessels of human tumors and less so than to vessels in normal tissue (page

380, 1st column, 2nd paragraph). The reference teaches phage display (phage are viruses that effect bacteria) of tripeptides that are targeted to tumor endothelial cells, the reference teaches the tripeptide RGD and NGR. The reference also teaches that tumor homing is more efficient with the NGR tripeptide. The reference does not teach inserting the tripeptides into an adenoviral vector.

It would have been obvious to one of ordinary skill in the at the time the invention was made to utilize a unique restriction site in an adenoviral vector in order to insert a foreign peptides into the HI fiber loop in order to alter the viruses tropism, ie. the ability to infect cells that are not within its natural range as taught Dmitriev et al. One having ordinary skill in the art would have been motivated to do this in view of the teachings of Arap et al. which show the tripeptide homing in a bacterial viral system which teaches that the NGD tripeptide is more efficient at tumor homing. Furthermore, it is well known in the art to utilize unique restriction sites that may be cloned into a vector for the ease of inserting gene sequences into the site. The key element is choosing a unique site as taught by Dmitriev et al., here the choice is based inserting a restriction site that is not present in the virus or peptide sequence. A scan of two adenoviral genomes indicted that there are several restriction sites that are not present in the adenovirus. These not only include Csp45I, Cla1 but also include VspI, Swa1, SmiI, PacI, BspDI, CpoI, Ban III, SrfI to name a few. Therefore, the specific choice of a unique restriction enzyme sequences such as Csp45I and/or ClaI would fall within the skills of an ordinary artisan because the choice is based on the sites that are not present in a particular viral sequence. If the choice of restriction enzyme produces an unexpected result, applicant needs to point out what the

unexpected results are. Therefore, the instant invention is obvious over Dmitriev et al. in view of Arap et al.

Conclusion

No claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for informal communications use 703-308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

ULRIKE WINKLER, PHD.
PATENT EXAMINER 8/25/03